

Health and Economic Impact of Sgl2 Inhibitors Compared With Conventional Glucose-Lowering Agents in Type 2 Diabetes Mellitus Patients with Cardiovascular Risk: A Literature Review

C Vaishnavidevi^{1*}, S Abinaya¹, P Abitha¹, Anupama Sankar¹

Department Of Pharmacy Practice, Swamy Vivekanandha College Of Pharmacy, Namakkal, Tamil Nadu.

Corresponding Author: C VAISHNAVIDEVI

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ABSTRACT

Sodium-glucose cotransporter-2 (SGLT2) inhibitors have emerged as a transformative therapeutic class in the management of type 2 diabetes mellitus (T2DM), particularly for patients with cardiovascular risk. This literature review comprehensively evaluates the health and economic impact of SGLT2 inhibitors compared with conventional glucose-lowering agents in T2DM patients with established cardiovascular disease or high cardiovascular risk. Evidence from landmark cardiovascular outcome trials including EMPA-REG OUTCOME, CANVAS Program, and DECLARE-TIMI 58 demonstrates that SGLT2 inhibitors significantly reduce major adverse cardiovascular events, hospitalization for heart failure, and progression of chronic kidney disease. Real-world evidence from studies such as CVD-REAL and EASEL confirms these benefits in routine clinical practice, showing substantial reductions in heart failure hospitalizations and all-cause mortality. Beyond glycemic control, the pleiotropic effects of SGLT2 inhibitors—including natriuresis, blood pressure reduction, weight loss, and improved myocardial energetics—contribute to their superior cardiorenal protective profile compared to traditional oral hypoglycemic agents. Although SGLT2 inhibitors entail higher initial medication costs, pharmacoeconomic analyses demonstrate favorable cost-effectiveness through reduced hospitalizations and delayed progression to end-stage renal disease, ultimately lowering long-term healthcare expenditures. This review synthesizes evidence from major randomized controlled trials and real-world studies, highlighting the dual clinical and economic benefits that position SGLT2 inhibitors as disease-modifying therapies in contemporary cardiometabolic care.

KEYWORDS: SGLT2 inhibitors, type 2 diabetes mellitus, cardiovascular disease, heart failure,

chronic kidney disease, cost-effectiveness, cardiovascular outcomes, empagliflozin, dapagliflozin

I. INTRODUCTION

Type 2 diabetes mellitus (T2DM) remains a significant global and national health problem, with India accounting for a considerable portion of the worldwide burden.¹ Individuals with T2DM frequently exhibit a higher risk for cardiovascular issues, resulting in cardiovascular diseases and complications being major contributors to illness and death rates among those with diabetes.² Therapies aimed at lowering glucose levels have historically depended on medications that mainly target hyperglycemia (such as metformin, sulfonylureas, insulin, DPP-4 inhibitors), which might not provide significant cardiovascular or renal protection apart from reducing blood sugar levels.³ In recent times, the group of SGLT2 inhibitors (SGLT2i) has arisen as a revolutionary alternative by decreasing renal glucose reabsorption, these medications reduce blood sugar levels and simultaneously activate positive cardiovascular effects.⁴ This "beyond-glucose" advantage makes SGLT2 inhibitors especially appealing for T2DM patients who have cardiovascular risk or current cardiovascular conditions. Assessing both the health outcomes (clinical results) and economic effects (expenses, cost-effectiveness) of SGLT2 inhibitors-in comparison to traditional glucose-lowering medications - is crucial, particularly in tertiary care hospitals with diverse socio-economic patient groups.⁵

CARDIOVASCULAR RISK IN DM PATIENTS

Cardiovascular disease (CVD) is a significant and prevalent concern linked to Type 2 Diabetes Mellitus (T2DM), continuing to be the

primary cause of illness and death in this demographic. Epidemiological research indicates that around one-third of people with T2DM have developed cardiovascular diseases, revealing a notably higher occurrence than in the general population.⁶ Individuals with T2DM face a two to four times elevated risk of having severe cardiovascular incidents such as myocardial infarction, Acute coronary syndrome, Pulmonary edema, stroke, and heart failure compared to those without diabetes.⁷ The increased risk stems from various interconnected elements, such as insulin resistance, persistently high blood sugar, dyslipidemia, systemic inflammation, oxidative stress, endothelial dysfunction, and rapid atherosclerosis. Diabetic dyslipidemia, marked by elevated triglycerides, reduced HDL cholesterol, and small dense LDL particles, worsens the development of atherogenesis and vascular damage.⁸ Moreover, conditions like hypertension, obesity, and chronic kidney disease often occur alongside T2DM and together elevate cardiovascular risk.⁹ Research shows that T2DM can result in heart complications both structurally and functionally, referred to as diabetic cardiomyopathy, regardless of coronary artery disease. successful glycemic control, the ongoing cardiovascular risk stays elevated, underscoring that diabetes is not just a metabolic condition but also a significant vascular illness.¹⁰ Hence, promptly identifying and managing cardiovascular risk factors is essential in T2DM care, especially when considering treatment choices and long-term health results.¹¹

SGLT2 INHIBITORS:

Oral antidiabetic drugs called SGLT2 inhibitors lower blood sugar levels by focusing on renal glucose reabsorption rather than insulin production or sensitivity. In the kidneys, glucose filtered by the glomerulus is normally reabsorbed in the proximal tubule via the SGLT2 transporter. By inhibiting this protein, SGLT2 inhibitors lower plasma glucose levels without changing insulin action or pancreatic β -cell function, therefore boosting urine glucose excretion (glucosuria). This makes them effective even in persons with insulin resistance or declining β -cell activity. Beyond glycemic control, they also lower blood pressure, safeguard the heart and kidneys, and help people lose weight. Due to these numerous advantages, SGLT2 inhibitors are advised in current diabetes recommendations, particularly for individuals with heart failure or chronic renal sickness.¹²⁻¹³

MECHANISM OF ACTION (MOA):

Selective Blockade: SGLT2 inhibitors specifically block the SGLT2 (Sodium-Glucose Cotransporter 2) protein, which is primarily responsible for reabsorbing about 90% of filtered glucose back into the bloodstream from the kidney tubules. **Increased Glucose Excretion:** By blocking this reabsorption pathway, the drugs cause a significant increase in the excretion of glucose in the urine (glucosuria).¹² **Insulin-Independent Effect:** This mechanism simply forces the kidneys to excrete excess glucose. Unlike medications such as sulfonylureas or insulin itself, SGLT2 inhibitors do not increase insulin release from the beta-cells. **Low Hypoglycemia Risk:** The medication usually only lowers blood glucose when it is high (hyperglycemia) since its action is limited to lowering the blood glucose level by excretion rather than forcing the body to generate or use more insulin. When blood glucose approaches a normal level, the amount of glucose filtered by the kidneys decreases, and the glucosuria effect diminishes, providing a self-limiting mechanism that protects against over-lowering the blood sugar (hypoglycemia), even in patients with underlying beta-cell dysfunction.¹³

CLINICAL BENEFIT:

SGLT2 inhibitors give diverse therapeutic advantages beyond glucose reduction. By boosting urine glucose excretion, these medicines often reduce HbA1c by roughly 0.5–1%. The caloric loss through glucosuria generally leads to weight reduction, which is favorable for overweight or obese people with type 2 diabetes. Mild diuretic and natriuretic effects contribute to moderate decreases in both systolic and diastolic blood pressure.¹⁴

Large-scale clinical trials and meta-analyses have showed convincing cardiovascular and renal benefits: reductions in hospitalization for heart failure, lower risk of major adverse cardiovascular events (MACE), and slowing of chronic kidney disease development. For instance, SGLT2 inhibitor medication has been associated with considerably lower rates of cardiovascular death and all-cause mortality compared to placebo or other medicines. Additionally, in individuals with diabetic kidney disease, these medications slow decline in glomerular filtration rate, reduce albuminuria, and lessen the risk of end-stage renal disease.¹⁵ The combination of glycemic control, weight and blood pressure reduction, and cardiorenal protection makes SGLT2 inhibitors a particularly effective tool in current diabetes

therapy.^{12,16}

COMPARATIVE CLINICAL OUTCOMES: SGLT2 INHIBITORS VS OTHER OHAS

Compared with typical oral hypoglycemic medicines, SGLT2 inhibitors demonstrate superior cardiovascular and renal outcomes. Clinical trials frequently reveal reductions in heart failure hospitalizations, slower progression of chronic renal illness, and decreased cardiovascular mortality. Metformin has negligible impact on the kidneys but modest cardiovascular protection. DPP-4 inhibitors demonstrate cardiovascular neutrality without renal benefit. Although sulfonylureas effectively lower blood sugar, they do not protect the heart or kidneys and raise the risk of hypoglycemia. TZDs enhance insulin sensitivity but may worsen edema and heart failure. GLP-1 receptor agonists show fewer renal-protective effects than SGLT2 inhibitors, but they do reduce severe atherosclerosis events. Overall, SGLT2 inhibitors produce the most robust long-term cardio-renal benefits.^{17,18}

GLYCEMIC CONTROL OUTCOME:

SGLT2 inhibitors improve glycemic control through an insulin-independent mechanism, which makes them effective throughout the course of type 2 diabetes. They do this by promoting glucose loss in urine, which lowers both fasting and postprandial glucose levels. This mechanism results in significant HbA1c reductions, usually without the risk of hypoglycemia unless combined with insulin or sulfonylureas. In addition to lowering blood glucose, reducing visceral adiposity, and lower blood pressure—factors that collectively support improved cardiometabolic health.¹⁹ SGLT2 inhibitors complement basal insulin regimens, incretin-based treatments, and the hepatic effect of metformin. Their metabolic advantages give evident superiority over sulfonylureas, which sometimes induce weight gain and unexpected hypoglycemia spells. Their cardiovascular and renal advantages endure even when the glycemic impact may diminish in advanced kidney failure. When contrasted with DPP-4 inhibitors, they often cause higher metabolic improvements coupled with broader clinical advantages. Overall, SGLT2 inhibitors provide lasting glycemic control while supporting weight management, metabolic balance, and long-term risk reduction.²⁰

CARDIOVASCULAR RESULTS

Among SGLT2 inhibitors' most prominent clinical advantages are those connected to the

cardiovascular system. Major adverse cardiovascular events (MACE) are routinely reduced in large-scale studies, especially with empagliflozin, which has demonstrated significant reductions in cardiovascular mortality. The substantial reduction in heart-failure hospitalizations, which frequently manifests within weeks of therapy commencement, is one of the most consistent findings throughout this pharmacological family. These advantages are ascribed to processes such as natriuresis, osmotic diuresis, decreased cardiac preload and afterload, enhanced myocardial energetics, and lower inflammation.²¹

SGLT2 inhibitors offer a notably protective cardiovascular profile when compared to other OHAs. Sulfonylureas may elevate the risk of hypoglycemia-related cardiac events, although DPP-4 inhibitors are generally neutral with regard to cardiovascular outcomes. Thiazolidinediones may aggravate fluid retention and contribute to heart-failure worsening. As a result, treatment recommendations for those with diabetes and pre-existing cardiovascular risk presently emphasize SGLT2 inhibitors. Their capacity to decrease heart-failure events, control cardiovascular development, and promote survival makes them a fundamental medication for cardiometabolic disease management.²²

HEALTH AND ECONOMIC IMPACT OF SGLT2 INHIBITORS

Sodium–glucose cotransporter-2 (SGLT2) inhibitors have significantly transformed the management of type 2 diabetes mellitus (T2DM), heart failure (HF), and chronic kidney disease (CKD) by demonstrating substantial clinical and economic benefits²³. Beyond glycemic control, these agents provide cardiorenal protection independent of baseline glycemic status²⁴.

Health Impact

Large cardiovascular outcome trials (CVOTs) have demonstrated that SGLT2 inhibitors reduce major adverse cardiovascular events (MACE), hospitalization for heart failure (HHF), and progression of renal disease. The EMPA-REG OUTCOME trial showed that empagliflozin reduced cardiovascular mortality by 38% and hospitalization for heart failure by 35% in patients with T2DM and established cardiovascular disease⁶. Similarly, the CANVAS Program demonstrated significant reductions in cardiovascular events and renal outcomes with canagliflozin⁷.

The DECLARE-TIMI 58 trial further

confirmed a significant reduction in hospitalization for heart failure and renal composite outcomes with dapagliflozin, even in a broader population including those without established cardiovascular disease⁸. In patients with heart failure with reduced ejection fraction (HFrEF), the DAPA-HF trial showed a 26% reduction in worsening heart failure or cardiovascular death irrespective of diabetic status²⁵. Moreover, the DAPA-CKD trial reported significant slowing of CKD progression and reduced renal and cardiovascular mortality⁹.

Mechanistically, SGLT2 inhibitors exert benefits through osmotic diuresis, natriuresis, reduction in intraglomerular pressure, improved myocardial metabolism, and reduction in inflammation and oxidative stress²⁴. These pleiotropic effects contribute to improved survival and reduced disease progression.

Economic Impact

Although SGLT2 inhibitors have higher upfront medication costs compared to conventional glucose-lowering therapies, they demonstrate favorable cost-effectiveness profiles due to reductions in hospitalizations and long-term complications²⁶. Several pharmaco-economic analyses have shown that empagliflozin and dapagliflozin are cost-effective in high-risk T2DM

populations when evaluated from healthcare system perspectives²⁷.

Reduction in heart failure hospitalizations significantly lowers direct medical expenditures, as heart failure admissions represent one of the largest contributors to diabetes-related healthcare costs²⁸. Additionally, delaying progression to end-stage renal disease (ESRD) reduces the need for dialysis and transplantation, leading to substantial long-term economic savings⁹.

Model-based economic evaluations indicate that SGLT2 inhibitors increase quality-adjusted life years (QALYs) while maintaining acceptable incremental cost-effectiveness ratios (ICERs), particularly in patients with established cardiovascular or renal disease²⁷. In real-world settings, reduced readmission rates further support their budgetary sustainability²⁸.

Overall Impact

Collectively, SGLT2 inhibitors provide dual health and economic benefits by reducing cardiovascular mortality, preventing heart failure hospitalizations, slowing CKD progression, and lowering long-term healthcare expenditures. Their expanding indications beyond glycemic control position them as disease-modifying agents rather than solely antidiabetic therapies.^{23,6,9}

Table 1. Major Randomized Controlled Trials of SGLT2 Inhibitors

Trial	Year	Population	Primary Outcome	Risk Reduction (%)
EMPA-REG OUTCOME⁶	2015	T2DM + CVD	3-point MACE	14%
CANVAS Program⁷	2017	T2DM + high CV risk	3-point MACE	14%
DECLARE-TIMI 58⁸	2019	T2DM ± CVD	CV death or HFrEF	17%
CREDESCENCE²⁹	2019	T2DM + CKD	Renal composite outcome	30%
VERTIS-CV³⁰	2020	T2DM + CVD	3-point MACE	3%
DAPA-HF²⁵	2019	HFrEF ± diabetes	CV death or worsening HF	26%
EMPEROR-Reduced³¹	2020	HFrEF	CV death or HF hospitalization	25%

EMPEROR-Preserved³²	2021	HFpEF	CV death or HF hospitalization	21%
DELIVER³³	2022	HFmrEF/HFpEF	CV death or worsening HF	18%
DAPA-CKD⁹	2020	CKD ± diabetes	Renal composite outcome	39%
EMPA-KIDNEY³⁴	2022	CKD ± diabetes	Kidney progression or CV death	28%

Table 2. Major Real-World Evidence Studies of SGLT2 Inhibitors

Study	Year	Population	Primary Outcome	Risk Reduction (%)
CVD-REAL³⁵	2017	T2DM (real-world cohort)	HHF	39%
EASEL³⁶	2018	T2DM + CVD	All-cause mortality	43%
OBSERVATION-4D³⁷	2019	T2DM routine practice	HF hospitalization	43%
DECLARE-HF analysis³⁸	(RW 2019)	T2DM + HF	HF hospitalization	37%
DAPA-HF extension³⁹	(RW 2021)	HFrEF	HF hospitalization	55%

II. CONCLUSION

Type 2 diabetes mellitus is now recognized as a major cardiometabolic disorder rather than a condition limited to hyperglycemia. Evidence from landmark trials such as **EMPA-REG OUTCOME**, **CANVAS Program**, and **DECLARE-TIMI 58** demonstrates that SGLT2 inhibitors significantly reduce cardiovascular events, heart failure hospitalizations, and progression of kidney disease. Beyond improving glycemic control, they provide meaningful survival benefits and favorable cost-effectiveness by lowering long-term complication-related expenses. Overall, SGLT2 inhibitors have emerged as disease-modifying therapies that address both the clinical and economic burden of type 2 diabetes, especially in patients with cardiovascular and renal risk.

III. FUTURE PERSPECTIVE

Future research is likely to focus on earlier initiation of SGLT2 inhibitors, broader use in non-diabetic heart failure and chronic kidney disease populations—as supported by trials like **DAPA-HF** and **EMPEROR-Preserved**—and development of personalized treatment strategies. More real-world and region-specific economic data, particularly from developing countries, will further clarify their long-term sustainability and accessibility. As evidence expands, SGLT2 inhibitors are expected to play an increasingly central role in integrated cardiometabolic care.

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